METHOD FOR THE PREPARATION OF HEXAHYDRO-FURO-[2,3-B]FURAN-3-OL

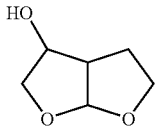
CROSS REFERENCE TO RELATED APPLICATIONS

This Application is a 35 U.S.C. § 371 national phase application of PCT/EP02/10062, with an international filing date of Sep. 6, 2002, which claims priority to application EP 01203416.1, filed on Sep. 10, 2001, all of which are incorporated herein by reference in their entirety.

The present invention relates to a method for the preparation of hexahydro-furo[2,3-b]furan-3-ol as well as novel intermediates for use in said method. More in particular the invention relates to a stereoselective method for the preparation of hexahydro-furo[2,3-b]furan-3-ol, and to a method amenable to industrial scaling up.

Hexahydro-furo[2,3-b]furan-3-ol is an important pharmacological moiety present in the structure of retroviral protease inhibitors such as those described in Ghosh et al. in *J. Med. Chem.* 1996, 39(17), 3278–3290, EP 0 715 618, WO 99/67417, and WO 99/65870. Said publications are hereby incorporated by reference.

Several methods for the preparation of hexahydro-furo[2,3-b]furan-3-ol (formula (7))



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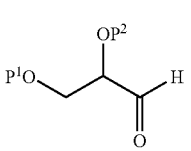
are known. Ghosh et al. in *J. Med. Chem.* 1996, 39(17), 3278–3290, describe an enantioselective synthesis to obtain both (3R,3aS,6aR) and (3S,3aR,6aS) hexahydro-furo[2,3-b]furan-3-ol in optically pure form starting from 3(R)-diethyl malate and 3(S)-diethyl malate respectively. This process comprises several steps such as an allylation step using lithium diisopropyl amide, followed by a reduction step, and further a Swern oxidation step followed by an ozonolytic cleavage and a hydroboration step using 9-borabicyclo[3.3.1]nonane (9-BBN). Ghosh et al. also disclose a racemic synthesis of both the (3R,3aS,6aR) and (3S,3aR,6aS) enantiomers of hexahydrofuro[2,3-]furan-3-ol followed by an enzymatic resolution of the final product. This latter synthesis starts from 2,3-dihydrofuran and comprises the step of treating said intermediate with N-iodosuccinimide and allyl alcohol followed by a radical cyclisation in the presence of a catalyst i.e. cobaloxime. An ozonolytic cleavage followed by a reduction step furnished the racemic hexahydro-furo[2,3-b]furan-3-ol. Optically active compound (3R,3aS,6aR) hexahydro-furo[2,3-b]furan-3-ol is obtained after enzymatic resolution followed by silica gel chromatography. Pezeck et al. *Tetrahedron Lett.* 1986, 27, 3715–3718 also describes a route for the synthesis of hexahydro-furo[2,3-b]-furan-3-ol using ozonolysis. Hexahydro-furo[2,3-b]furan-3-ol is also described as an intermediate in the synthesis of optically active perhydrofuro[2,3-b]furan derivatives (Uchiyama et al., *Tetrahedron Lett.* 2001, 42, 4653–4656.). The key step in this procedure is the oxyselenenylation of 2,3-dihydrofuran. This procedure is suitable for use at the laboratory level, yet not amenable for scaling up. Although the two synthetic routes described by Ghosh et al. provide (3R,3aS,6aR) and (3S,3aR,6aS) hexahydro-furo[2,3-b]furan-3-ol in reasonable yields and high enantiomeric excess, they both are only feasible on a laboratory scale, but, for a number of reasons, are not amenable to industrial scaling up. For example, these known routes suffer from the disadvantage of utilizing expensive materials, heavy metals and rare compounds, such as the N-iodosuccinimide, the catalyst cobaloxime, lithium diisopropyl amide and 9-BBN. The necessary ozonolysis step has the disadvantage of producing highly reactive and shock-sensitive ozonides and peroxides making this step too dangerous to be applied on industrial scale. Furthermore ozonolysis as well as Swern oxidation are highly exothermic and, as a consequence, have to be performed at very low temperatures. The racemic route needs an enzymatic resolution in the final step of the synthesis followed by silica gel purification. Furthermore, the racemic route suffers from the disadvantage of a low overall mass balance, originating from the fact that the resolution step, leading to the final enantiomerically pure compound, occurs in the last step of the synthesis whereby only a maximum of 50% yield of desired enantiomer can be obtained. Both art-known routes also produce a lot of waste such as solvents and salts in washings operations. Thus, these known methods are not suitable for the production of optically pure stereoisomers of hexahydro-furo[2,3-b]furan-3-ol on an industrial scale.

The main object of the present invention is to provide an improved method for producing hexahydro-furo[2,3-b]furan-3-ol, when compared to the art-known methods and their drawbacks. It is another object to provide a method for the synthesis of hexahydro-furo[2,3-b]furan-3-ol, which is suitable for industrial scaling-up. A further object of the present invention is to provide with a stereoselective method comprising steps wherein the stereochemistry of intermediates or final compounds is controlled, which allows the synthesis of the stereoisomers of hexahydro-furo[2,3-b]furan-3-ol. Another further object is to provide with a method which allows the production of hexahydro-furo[2,3-b]furan-3-ol in a overall yield equal or higher than for the above-described methods and with an enantiomeric excess higher than 50%. Another object of the present invention is to provide with a process for manufacturing hexahydro-furo[2,3-b]furan-3-ol which is produced from readily available starting materials and reagents. Another object of the present invention is to provide with novel intermediate compounds, which are useful as precursors in the synthesis of hexahydro-furo[2,3-]furan-3-ol.

The authors of the present invention have surprisingly found a novel and inventive method for the synthesis of stereoisomeric mixtures or stereoisomerically pure forms of hexahydro-furo[2,3-b]furan-3-ol.

Thus, the present method involves the synthesis of hexahydro-furo[2,3-b]furan-3-ol starting from an intermediate of formula (1) wherein P^1 and P^2 represent each independently a hydrogen, a hydroxy-protecting group or may together form a vicinal-diol protecting group, transforming said intermediate of formula (1) into a nitromethane



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derivative of formula (3) wherein R^1 represents alkyl, aryl or aralkyl, R^2 represents hydrogen or C(=O)OR^3, R^3 repre-